European Journal of Medicinal Chemistry 45 (2010) 1206–1210

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Short communication

Synthesis, characterization and biological activity of some new 1,3,4-oxadiazole bearing 2-flouro-4-methoxy phenyl moiety

B. Chandrakantha [a], Prakash Shetty [b], Vijesh Nambiyar [c], Nishitha Isloor [d], Arun M. Isloor [c,*]

[a] Syngene International Ltd, Biocon Park, Plot Nos. 2 and 3, Bommasandra 4th Phase, Jigani Link Road, Bangalore 560 100, India
[b] Department of Printing and Media Engineering, Manipal Institute of Technology, Manipal University, 576 104, India
[c] Department of Chemistry, National Institute of Technology, Surathkal, Mangalore 575 025, India
[d] Chemical Engineering Department, Biotechnology Division, National Institute of Technology, Surathkal, Mangalore 575 025, India

ARTICLE INFO

Article history:
Received 13 July 2009
Received in revised form
13 November 2009
Accepted 20 November 2009
Available online 4 December 2009

Keywords:
1,3,4-Oxadiazole
Antibacterial study
Antifungal study

ABSTRACT

In the present study a series of new 1,3,4-oxadiazole derivatives containing 2-fluoro-4-methoxy moiety were synthesized. These newly synthesized compounds were characterized by NMR, mass spectral, IR spectral study and also by C, H, N analyses. All the newly synthesized compounds were screened for their antibacterial and antifungal studies. Antimicrobial studies revealed that compounds **4a** and **4b** showed significant antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa* Compound **4i** showed significant antifungal activity against *C. albicans*.

1. Introduction

1,3,4-Oxadiazole is a versatile lead molecule for designing potential bioactive agents. The 1,3,4-oxadiazole derivatives have been found to exhibit diverse biological activities such as antimicrobial [1], anti-HIV [1], antitubercular [2], antimalarial [3], analgesic [4], anti-inflammatory [5], anticonvulsant [6], hypoglycemic [7] and other biological properties such as genotoxic studies [8] and lipid peroxidation inhibitor [9].

Used extensively in the symptomatic treatment of rheumatic fever, arthritis [10] (rheumatoid, osteo and Jaundice arthritis), myocardial infarctions and management of primary dysmenorrheal [11]. The major side effects in the use of aryl alkanoic acids is their gastric irritation, which is partly due to the corrosive nature of carboxylic acid group present in them. In order to reduce or mask the side effects of carboxylic moiety we planned to synthesize different 2,5-disubstituted-1,3,4-oxadiazoles (**4a–m**) via the condensation of 4-hydroxybenzohydrazide with various aromatic acids in presence of phosphorus oxychloride respectively in the hope of getting potent biodynamic agents and evaluate their antimicrobial activity.

Further fluorine containing molecules showed wide spectrum antimicrobial and biological properties. Keeping in view of these and in continuation of our research on biologically active molecules, we hereby report the synthesis of some novel 1,3,4-oxadiazoles containing 2-fluoro-4-methoxy phenyl containing moieties.

2. Chemistry

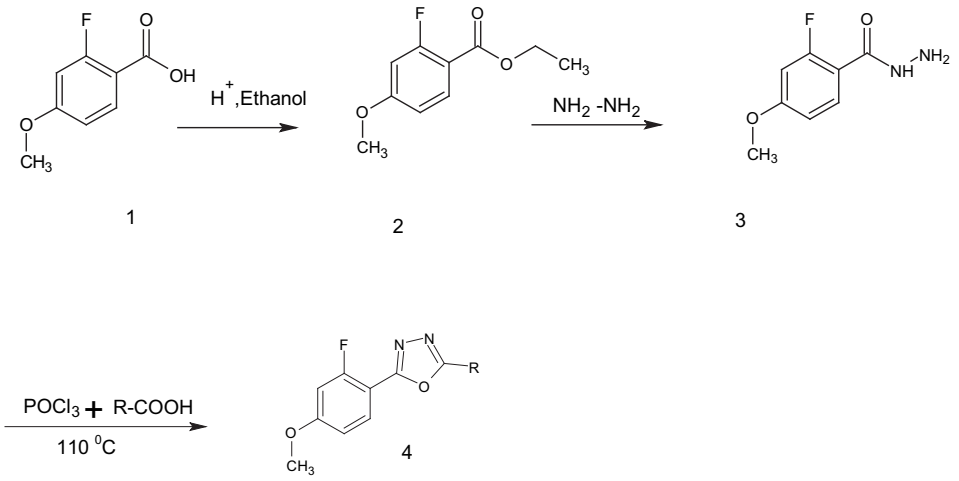
2-Fluoro-4-methoxybenzoic acid was converted into ethyl 2-fluoro-4-methoxybenzoate **2**, by the esterification reaction using known procedure [12]. Further this ester was converted into 2-fluoro-4-methoxybenzohydrazide **3**, by reacting with hydrazine hydrate in ethanol medium. Title compounds 2-(2-fluoro-4-methoxyphenyl)-5-substituted-1,3,4-oxadiazoles were synthesized by refluxing equimolar mixture of 2-fluoro-4-methoxybenzohydrazide **3,** with different aromatic carboxylic acid **(a–m)** in phosphorous oxychloride (10 vol) for 3 h (Scheme 1).

3. Antimicrobial studies

All the newly synthesized oxadiazoles were screened for their antibacterial and antifungal activity. For antibacterial studies microorganisms employed were *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa*. For antifungal, *Candida albicans* was used as organism. Both microbial studies were assessed by Minimum Inhibitory Concentration (MIC) by serial dilution

* Corresponding author. Fax: +91 824 2474033.
E-mail address: isloor@yahoo.com (A.M. Isloor).

0223-5234/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2009.11.046



Scheme 1. Scheme for synthesis of the new oxadiazoles.

method [13]. For this, the compound whose MIC has to be determined is dissolved in serially diluted DMF. Then a standard drop of the culture prepared for the assay is added to each of the dilutions, and incubated for 16–18 h at 37 °C. MIC is the highest dilution of the compound, which shows clear fluid with no development of turbidity.

4. Results and discussion

Formation of 2-(2-fluoro-4-methoxyphenyl)-5-substituted-1,3,4-oxadiazoles was confirmed by recording their IR, ^{1}H NMR and mass spectra. IR spectrum of oxadiazole **4a** showed absorption at 3097 cm^{-1} which is due to the aromatic stretching. An absorption band at 1594 cm^{-1} is due to the C═N group, band at 1057 cm^{-1} is due to stretching of oxadiazole ring and the absorption band appeared at 1093 cm^{-1} is due to C–F group.

The ^{1}H NMR spectrum of **4a** showed multiplet in the region of δ, 8.07–7.00. δ, 8.07 is due to aromatic proton, δ, 8.04–8.01 appeared as doublet of two protons, δ, 8.0–7.9 as doublet of one proton and triplet appeared at δ, 7.39 is due to the single proton. Similarly a singlet appeared at δ, 2.73 is due to the three protons of the methoxy group.

The mass spectrum of **4a** showed molecular ion peak at *m*/*z* 364, which is in agreement with the molecular formula $C_{16}H_{12}BrFN_2O_2$. Similarly the spectral values for all the compounds and C, H, N analyses are given in the experimental part.

5. Conclusions

A series of novel 2-(2-fluoro-4-methoxyphenyl)-5-substituted-1,3,4-oxadiazoles were synthesized and characterized by ^{1}H NMR, Mass spectrometry and IR studies. All the newly synthesized compounds were screened for their antibacterial and antifungal activity. Among the screened samples, compounds **4a** and **4b** showed excellent antibacterial activity against *E. coli* and *P. aeruginosa* even at low concentration of 3 μg/ml. Compound **4a** has 3-bromo-2-methyl phenyl group and **4b** has 2,3,4-trifluoro phenyl group as substituents. Remaining compounds have showed significant antibacterial activity. Antifungal screening was carried out on *C. albicans*. Among the tested compounds, **4i** and **4k** showed highest inhibition at 3 μg/ml concentration. **4i** has 2-bromo-5-chloro phenyl group and **4k** has 5-methylisoxazole groups respectively (Table 1). All the newly synthesized compounds have 2-fluoro-4-methoxy phenyl substituents, which is accounted for their significant antimicrobial activity.

6. Experimental

Melting points were determined by open capillary method and were uncorrected. Elemental analysis was performed on Thermo Finningan FLASH EA 1112 CHN analyzer. The IR spectra (In KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. ^{1}H NMR spectra were recorded on a Perkin–Elmer EM 300 MHz spectrometer using TMS as internal standard. Mass spectra were recorded on LC–MS-Aglilent 1100 series with MSD (Ion trap) using 0.1% aqueous TFA in acetonitrile system on C18-BDS column for 10 min duration. Ionization mode is EI for all the compounds. Purity of the compounds was checked by TLC silica coated plates obtained from Merck.

6.1. Preparation of ethyl 2-fluoro-4-methoxybenzoate (**2**)

To a mixture of 2-fluoro-4-methoxybenzoic acid (10 g, 0.0587 mol) in Ethanol (100 ml) was added conc. Sulphuric acid (1 ml) and refluxed for 5 h. The reaction mixture was concentrated the solid separated was filtered, washed with water and recrystallised with ethanol to give **2** as white crystals. (10 g, 85%) Mp. 158–160 °C.

6.2. Preparation of 2-fluoro-4-methoxybenzohydrazide (**3**)

A mixture of ethyl 2-fluoro-4-methoxybenzoate (10 g, 0.0602 mol) and hydrazine hydrate (5.0 ml, 0.1009 mol) in ethanol (100 ml) was heated under reflux for 8 h. The reaction mixture was

Table 1
Antibacterial and antifungal data for the newly synthesized oxadiazoles.

Compound No.	Antibacterial activity data in MIC (μg/ml)				Antifungal activity data in MIC (μg/ml)
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*
4a	6	6	3	3	6
4b	6	6	3	3	6
4c	6	6	6	6	6
4d	6	6	6	6	6
4e	6	6	6	12.5	6
4f	12.5	6	6	12.5	6
4g	6	6	12.5	6	6
4h	6	6	12.5	6	6
4i	6	6	6	6	3
4j	6	6	6	6	6
4k	12.5	12.5	6	6	3
4l	6	6	6	6	6
4m	6	6	6	6	6
Furacin (Std)	12.5	12.5	6	12.5	Flucanazol (Std) 6
DMF (Control)	–	–	–	–	–

concentrated and left to cool. The solid product obtained was filtered, washed with water and recrystallised with ethanol to give **3** as white crystals. (7 g, 74%) Mp. 158–160 °C.

6.3. General procedure for preparation of 2-(2-fluoro-4-methoxyphenyl)-5-substituted 1,3,4-oxadiazole (**4**)

An equimolar mixture of Acid hydrazide **3** with different aromatic carboxylic acid (a–e) was refluxed with phosphorous oxychloride (10 vol) for 2–3 h. Reaction mixture was concentrated through rotovap, the residue was quenched with ice water and the solid separated was filtered off, washed with water and further purified by recrystallization with ethanol to afford 5-substituted 1,3,4-oxadiazole bearing 2-fluoro-4-methoxy phenyl moiety as white crystalline solid.

6.4. Preparation of 2-(3-bromo-2-methylphenyl)-5-(2-fluoro-4-methoxyphenyl)-1,3,4-oxadiazole (**4a**)

To a mixture of 2-fluoro-4-methoxybenzohydrazide 1 (1 g, 0.0054 mol) and 3-bromo 2-methyl benzoic acid (1.16 g, 0.0054 mol) was added phosphorous oxychloride (10 ml). The reaction mixture was refluxed at 100 °C for 2 h. The reaction mixture was cooled to room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice and the solid separated was filtered and dried through pump to afford title compound **4a** as white solid. (1.5 g, 78%); mp 290–295 °C; IR (KBr) cm^{-1} 3097 (Ar-H), C=N (1594), C=C (1560), C–O (1057, stretch of oxadiazole ring), C–F (1093); mass *m*/*z* (M^+) 364: ^{1}H NMR (300 MHz-DMSO-d_6-ppm) δ 8.02–8.07 (m, 1H, Ar-H), 7.95–7.98 (d, 1H, Ar-H, $J = 7.8$ Hz), 7.87–7.89 (d, 1H, Ar-H, $J = 7.14$ Hz), 7.34–7.39 (m, 1H, Ar-H), 7.10–7.16 (dd, 1H, Ar-H, $J = 2.4$ Hz), 7.00–7.04 (dd, 1H, Ar-H, $J = 2.31$ Hz), 3.87 (s, 3H, $-OCH_3$), 2.73 (s, 3H, $-CH_3$). Anal. found (calc.) for $C_{16}H_{12}BrFN_2O_2$ (%): C, 53.01 (52.91); H, 3.45 (3.29); N, 7.96 (7.8).

6.5. Preparation of 2-(2-fluoro-4-methoxyphenyl)-5-(2,3,4-trifluorophenyl)-1,3,4-oxadiazole (**4b**)

To a mixture of 2-fluoro-4-methoxybenzohydrazide 1 (1 g, 0.0054 mol) and 2,3,4-trifluorobenzoic acid (0.95 g, 0.0054 mol) was added phosphorous oxychloride (10 ml). The reaction mixture was refluxed at 100 °C for 2 h. The reaction mixture was cooled to room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice and the solid separated was filtered and dried through pump to afford title compound **4b** as white solid. (1.6 g, 90%); mp 235–238 °C; IR (KBr) cm^{-1} 3070 (Ar-H), C=N (1585), C=C (1580), C–O (1040, stretch of oxadiazole ring), C–F (1090); mass *m*/*z* (M^+) 325: ^{1}H NMR (300 MHz-DMSO-d_6-ppm) δ 8.04–8.09 (t, 1H, Ar-H, $J = 8.5$ Hz), 7.91–7.93 (m, 1H, Ar-H), 7.15–7.19 (m, 1H, Ar-H), 6.77–6.89 (m, 2H, Ar-H), 3.9 (s, 3H, $-OCH_3$). Anal. Found (calc.) for $C_{15}H_8F_4N_2O_2$ (%): C, 55.65 (55.56); H, 2.60 (2.47); N, 8.78 (8.64).

6.6. Preparation of 2-(2-fluoro-4-methoxyphenyl)-5-[2-(trifluoromethyl) phenyl]-1,3,4-oxadiazole (**4c**)

To a mixture of 2-fluoro-4-methoxybenzohydrazide 1 (1 g, 0.0054 mol) and 2-trifluoromethyl benzoic acid (1.026 g, 0.0054 mol) was added phosphorous oxychloride (10 ml). The reaction mixture was refluxed at 100 °C for 2 h. The reaction mixture was cooled to room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice and the solid separated was filtered and dried through pump to afford title compound **4c** as white solid. (1.5 g, 81%); mp 222–228 °C; IR (KBr) cm^{-1} 3070 (Ar-H), C=N (1545), C=C (1560), C–O (1070, stretch of oxadiazole ring), C–F (1050); mass *m*/*z* (M^+) 339: ^{1}H NMR (400 MHz-DMSO-d_6-ppm). δ 8.34–8.39 (m, 2H, Ar-H), 8.07–8.11 (m, 1H, Ar-H), 7.81–7.83 (m, 1H, Ar-H), 7.67–7.71 (m, 1H, Ar-H), 6.79–6.89 (dd, 2H, Ar-H, $J = 8.8$ Hz), 3.9 (s, 3H, $-OCH_3$). Anal. Found (calc.) for $C_{16}H_{10}F_4N_2O_2$ (%): C, 57.01 (56.91); H, 2.18 (3.00); N, 8.43 (8.3).

6.7. Preparation of 3-[5-(2-fluoro-4-methoxyphenyl)-1,3,4-oxadiazol-2-yl] benzonitrile (**4d**)

To a mixture of 2-fluoro-4-methoxybenzohydrazide 1 (1 g, 0.0054 mol) and 3-cyanobenzoic acid (0.8053 g, 0.0054 mol) was added phosphorous oxychloride (10 ml). The reaction mixture was refluxed at 100 °C for 2 h. The reaction mixture was cooled to room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice and the solid separated was filtered and dried through pump to afford title compound **4d** as white solid. (1.5 g, 81%); mp 222–228 °C; IR (KBr) cm^{-1} 3030 (Ar C-H), C=N (1615), C=C (1540), C–O (1060, stretch of oxadiazole ring), C–F (1070); mass *m*/*z* (M^+) 296: ^{1}H NMR (400 MHz-DMSO-d_6-ppm). δ 8.39–8.41 (m, 2H, Ar-H), 8.11–8.17 (m, 2H, Ar-H), 7.82–7.86 (m, 1H, Ar-H), 7.14–7.18 (dd, 1H, Ar-H, $J = 2.4$ Hz), 7.03–7.06 (dd, 1H, Ar-H, $J = 2.4$ Hz), 3.89 (s, 3H, $-OCH_3$). Anal. Found (calc.) for $C_{16}H_{10}FN_3O_2$ (%): C, 65.29 (65.09); H, 3.51 (3.39); N, 14.23 (14.44).

6.8. Preparation of 2-(2,3-dimethylphenyl)-5-(2-fluoro-4-methoxyphenyl)-1,3,4-oxadiazole (**4e**)

To a mixture of 2-fluoro-4-methoxybenzohydrazide 1 (1 g, 0.0054 mol) and 2,3-dimethyl benzoic acid (0.8109 g, 0.0054 mol) was added phosphorous oxychloride (10 ml). The reaction mixture was refluxed at 100 °C for 2 h. The reaction mixture was cooled to room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice and the solid separated was filtered and dried through pump to afford title compound **4e** as white solid. (1.5 g, 92%); mp 222–228 °C; IR (KBr) cm^{-1} 3020 (Ar C-H), C=N (1615), C=C (1540), C–O (1060, stretch of oxadiazole ring), C–F (1070); mass *m*/*z* (M^+) 299: ^{1}H NMR (300 MHz-DMSO-d_6-ppm). δ 8.04–8.10 (t, 1H, Ar-H, $J = 8.52$ Hz), 7.80–7.82 (d, 1H, Ar-H, $J = 7.59$ Hz), 7.24–7.35 (m, 2H, Ar-H) 6.76–6.88 (m, 2H, Ar-H), 3.89 (s, 3H, $-OCH_3$), 2.65 (s, 3H, $-CH_3$), 2.40 (s, 3H, $-CH_3$). Anal. Found (calc.) for $C_{17}H_{15}FN_2O_2$ (%): C, 68.65 (68.55); H, 5.38 (5.09); N, 9.64 (9.50).

6.9. Preparation of 2-chloro-5-[5-(2-fluoro-4-methoxyphenyl)-1,3,4-oxadiazol-2-yl] pyridine (**4f**)

To a mixture of 2-fluoro-4-methoxybenzohydrazide 1 (1 g, 0.0054 mol) and 6-chloronicotinic acid (0.84 g, 0.0054 mol) was added phosphorous oxychloride (10 ml). The reaction mixture was refluxed at 100 °C for 2 h. The reaction mixture was cooled to room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice and the solid separated was filtered and dried through pump to afford title compound **4f** as white solid. (1.5 g, 90%); mp 224–235 °C; IR (KBr) cm^{-1} 3030 (Ar C-H), C=N (1625), C=C (1560), C–O (1080, stretch of oxadiazole ring), C–F (1040), C–Cl (833); mass *m*/*z* (M^+) 306: ^{1}H NMR (300 MHz-DMSO-d_6-ppm) δ 9.08–9.09 (d, 1H, Ar-H, $J = 2.4$ Hz), 8.47–8.50 (dd, 1H, Ar-H, $J = 1.98$ Hz), 8.07–8.13 (t, 1H, Ar-H, $J = 8.61$ Hz), 7.78–7.80 (d, 1H, Ar-H, $J = 8.4$ Hz), 7.12–7.17 (dd, 1H, Ar-H, $J = 11.2$ Hz), 7.01–7.05 (dd, 1H, Ar-H, $J = 8.73$ Hz), 3.88 (s, 3H,

–OCH_3). Anal. Found (calc.) for $C_{14}H_9ClFN_3O_2$ (%): C, 55.61 (55.9); H, 3.17 (3.01); N, 13.35 (13.0).

6.10. Preparation of 2-(2,3-difluoro-6-nitrophenyl)-5-(2-fluoro-4-methoxyphenyl)-1,3,4-oxadiazole (**4g**)

To a mixture of 2-fluoro-4-methoxybenzohydrazide 1 (1 g, 0.0054 mol) and 5,6-difluoro-2-nitrobenzoic acid (1.1 g, 0.0054 mol) was added phosphorous oxychloride (10 ml). The reaction mixture was refluxed at 100 °C for 2 h. The reaction mixture was cooled to room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice and the solid separated was filtered and dried through pump to afford title compound **4g** as white solid. (1.7 g, 89%); mp 200–203 °C; IR (KBr) cm^{-1} 3040 (Ar C-H), C=N (1645), C=C (1540), C–O (1070, stretch of oxadiazole ring), C–F (1070); mass m/z (M^+) 352: ^{1}H NMR (400 MHz-DMSO d_6-ppm). δ 8.59–8.63 (dd, 1H, Ar-H, $J = 7.2$ Hz), 8.33–8.38 (dd, 1H, Ar-H, $J = 7.2$ Hz), 7.99–8.04 (t, 1H, Ar-H, $J = 7.6$ Hz), 7.14–7.18 (d, 1H, Ar-H, $J = 15$ Hz), 7.039–7.07 (dd, 1H, Ar-H, $J = 2.4$ Hz), 3.88 (s, 3H, –OCH_3). Anal. Found (calc.) for $C_{15}H_8F_3N_3O_4$ (%): C, 51.44 (51.3); H, 2.56 (2.4); N, 11.46 (11.3).

6.11. Preparation of 2-(4-fluorophenyl)-5-(2-fluoro-4-methoxyphenyl)-1,3,4-oxadiazole (**4h**)

To a mixture of 2-fluoro-4-methoxybenzohydrazide 1 (1 g, 0.0054 mol) and 4-fluoro benzoic acid (0.76 g, 0.0054 mol) was added phosphorous oxychloride (10 ml). The reaction mixture was refluxed at 100 °C for 2 h. The reaction mixture was cooled to room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice and the solid separated was filtered and dried through pump to afford title compound **4h** as white solid. (1.4 g, 90%); mp 210–212 °C; IR (KBr) cm^{-1} 3030 (Ar C-H), C=N (1635), C=C (1530), C–O (1030, stretch of oxadiazole ring), C–F (1060); mass m/z (M^+) 289: ^{1}H NMR (300 MHz-DMSO d_6-ppm). δ 8.07–8.16 (m, 3H, Ar-H), 7.44–7.50 (m, 2H, Ar-H), 7.11–7.16 (dd, 1H, Ar-H, $J = 2.4$ Hz), 7.0–7.04 (dd, 1H, Ar-H, $J = 2.4$ Hz), 3.87 (s, 3H, –OCH_3). Anal. Found (calc.) for $C_{15}H_{10}F_2N_2O_2$ (%): C, 61.65 (61.3); H, 3.66 (3.48); N, 9.72 (9.8).

6.12. Preparation of 2-(2-bromo-5-chlorophenyl)-5-(2-fluoro-4-methoxyphenyl)-1,3,4-oxadiazole (**4i**)

To a mixture of 2-fluoro-4-methoxybenzohydrazide 1 (1 g, 0.0054 mol) and 2-bromo-5-chloro benzoic acid (1.27 g, 0.0054 mol) was added phosphorous oxychloride (10 ml). The reaction mixture was refluxed at 100 °C for 2 h. The reaction mixture was cooled to room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice and the solid separated was filtered and dried through pump to afford title compound **4i** as white solid. (1.9 g, 90%); mp 215–218 °C; IR (KBr) cm^{-1} 3020 (Ar C-H), C=N (1625), C=C (1540), C–O (1040, stretch of oxadiazole ring), C–F (1065); mass m/z (M^+) 382: ^{1}H NMR (400 MHz-DMSO-d_6-ppm) δ 8.03–8.08 (m, 1H, Ar-H), 8.00–8.03 (d, 1H, Ar-H, $J = 7.8$ Hz), 7.82–7.84 (d, 1H, Ar-H, $J = 7.0$ Hz), 7.38–7.43 (m, 1H, Ar-H), 7.12–7.18 (dd, 1H, Ar-H, $J = 2.4$ Hz), 7.00–7.04 (dd, 1H, Ar-H, $J = 2.31$ Hz), 3.88 (s, 3H, –OCH_3). Anal. Found (calc.) for $C_{15}H_9BrClFN_2O_2$ (%): C, 46.97 (47.0); H, 2.36 (2.5); N, 7.30 (7.2).

6.13. Preparation of 3-[5-(2-fluoro-4-methoxyphenyl)-1,3,4-oxadiazol-2-yl] quinoline (**4j**)

To a mixture of 2-fluoro-4-methoxy benzohydrazide 1 (1 g, 0.0054 mol) and quinoline-3-carboxylic acid (0.94 g, 0.0054 mol) was added phosphorous oxychloride (10 ml). The reaction mixture was refluxed at 100 °C for 2 h. The reaction mixture was cooled to room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice and the solid separated was filtered and dried through pump to afford title compound **4j** as white solid. (1.5 g, 86%); mp 255–259 °C; IR (KBr) cm^{-1} 3020 (Ar C-H), C=N (1625), C=C (1520), C–O (1020, stretch of oxadiazole ring), C–F (1050); mass m/z (M^+) 322: ^{1}H NMR (300 MHz-DMSO-d6-ppm) δ 9.65 (s, 1H, Ar-H), 8.89 (s, 1H, Ar-H), 8.10–8.22 (m, 2H, Ar-H) 7.98–8.01 (m, 1H, Ar-H), 7.67–7.85 (m, 2H, Ar-H), 6.80–6.91 (m, 2H, Ar-H), 3.88 (s, 3H, –OCH_3). Anal. found (calc.) for $C_{18}H_{12}FN_3O_2$ (%): C, 67.29 (67.5); H, 3.76 (3.6); N, 13.08 (13.2).

6.14. Preparation of 2-(2-fluoro-4-methoxyphenyl)-5-(5-methylisoxazol-3-yl)-1,3,4-oxadiazole (**4k**)

To a mixture of 2-fluoro-4-methoxy benzohydrazide 1 (1 g, 0.0054 mol) and 5-methylisoxazole-3-carboxylic acid (0.68 g, 0.0054 mol) was added phosphorous oxychloride (10 ml). The reaction mixture was refluxed at 100 °C for 2 h. The reaction mixture was cooled to room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice and the solid separated was filtered and dried through pump to afford title compound **4k** as white solid. (1.2 g, 80%); mp 215–218 °C; IR (KBr) cm^{-1} 3090 (Ar C-H), C=N (1655), C=C (1550), C–O (1090, stretch of oxadiazole ring), C–F (1050), C=O (1643); mass m/z (M^+) 275: ^{1}H NMR (300 MHz-DMSO-d_6-ppm) δ 9.18 (s, 1H, Ar-H), 7.99–8.05 (t, 1H, Ar-H, $J = 8.64$ Hz), 7.11–7.15 (m, 2H, Ar-H), 3.8 (s, 3H, –OCH_3), 2.80 (s, 3H, –CH_3). Anal. found (calc.) for $C_{13}H_{10}FN_3O_3$ (%): C, 56.65 (56.73); H, 3.86 (3.66); N, 15.5 (15.3).

6.15. Preparation of 2-(2-fluoro-4-methoxyphenyl)-5-(3-fluoro-4-nitrophenyl)-1,3,4-oxadiazole (**4l**)

To a mixture of 2-fluoro-4-methoxy benzohydrazide 1 (1 g, 0.0054 mol) and 3-fluoro-4-nitrobenzoic acid (0.99 g, 0.0054 mol) was added phosphorous oxychloride (10 ml). The reaction mixture was refluxed at 100 °C for 2 h. The reaction mixture was cooled to room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice and the solid separated was filtered and dried through pump to afford title compound **4l** as white solid. (1.8 g, 99.45%); mp 235–235 °C; IR (KBr) cm^{-1} 3070 (Ar C-H), C=N (1697), C=C (1570), C–O (1054, stretch of oxadiazole ring), C–F (1084); mass m/z (M^+) 334: ^{1}H NMR (400 MHz-DMSO-d6-ppm) δ 8.37–8.41 (t, 1H, Ar-H, $J = 8$ Hz), 8.25–8.28 (d, 1H, Ar-H, $J = 11.2$ Hz), 8.11–8.16 (m, 2H, Ar-H), 7.14–7.17 (dd, 1H, Ar-H, $J = 12.4$ Hz), 7.04–7.06 (dd, 1H, Ar-H, $J = 8.8$ Hz), 3.8 (s, 3H, –OCH_3). Anal. found (calc.) for $C_{15}H_9F_2N_3O_4$ (%): C, 54.23 (54.0); H, 3.12 (3.0); N, 12.81 (12.7).

6.16. Preparation of 2-(3,5-difluorophenyl)-5-(2-fluoro-4-methoxyphenyl)-1,3,4-oxadiazole (**4m**)

To a mixture of 2-fluoro-4-methoxy benzohydrazide 1 (1 g, 0.0054 mol) and 3,5 diflurobenzoic acid (0.85 g, 0.0054 mol) was added phosphorous oxychloride (10 ml). The reaction mixture was refluxed at 100 °C for 2 h. The reaction mixture was cooled to room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice and the solid separated was filtered and dried through pump to afford title compound **4m** as white solid. (1.4 g, 87%); mp 265–269 °C; IR (KBr) cm^{-1} 3070 (Ar C-H), C=N (1675), C=C (1576), C–O (1054, stretch of oxadiazole ring), C–F (1083); mass m/z (M^+) 307: ^{1}H NMR (300 MHz-DMSO-d_6-ppm) δ 8.10–8.16 (t, 1H, Ar-H, $J = 8.64$ Hz), 7.78–7.81 (m, 2H, Ar-H), 7.57–7.64 (m, 1H, Ar-H) 7.12–7.17 (dd, 1H, Ar-H, $J = 2.4$ Hz), 7.01–7.05 (dd,

1H, Ar-H, $J = 2.52$ Hz) 3.88 (s, 3H, $-OCH_3$). Anal. found (calc.) for $C_{15}H_9F_3N_2O_2$ (%): C, 58.43 (58.8); H, 3.16 (2.96); N, 9.34 (9.2).

Acknowledgements

AMI is thankful to Director, NITK Surathkal, India for providing research facilities and also to Board of Research in Nuclear Sciences, Department of Atomic Energy, Government of India for YOUNG SCIENTIST award. C.B is thankful to Dr. John Kallikat and Premsai Rai. N of Syngene International Ltd. Bangalore, India, for their encouragement.

References

[1] A.A. El-Emam, O.A. Al-Deeb, M. Al-Omar, J. Lehmann, Bioorg. Med. Chem. 12 (2004) 5107–5113.
[2] S.G. Kucukguzel, E.E. Oruc, S. Rollas, F. Sahin, A. Ozbek, Eur. J. Med. Chem. 37 (3) (2002) 197–206.
[3] P.R. Kagthara, N.S. Shah, R.K. Doshi, H.H. Parekh, Indian J. Chem. 38B (1999) 572–576.
[4] M. Akhter, A. Husain, B. Azad, M. Ajmal, Eur. J. Med. Chem. 44 (2009) 2372–2378.
[5] P.C. Unangast, G.P. Shrum, D.T. Conner, C.D. Dyer, D.J. Schrier, J. Med. Chem. 35 (1992) 3691–3698.
[6] M.S.Y. Khan, R.M. Khan, S. Drabu, Indian J. Heterocycl. Chem. 11 (2001) 119–122.
[7] J.B. O'Neal, H. Rosen, P.B. Russell, A.C. Adams, A. Blumenthal, J. Med. Chem. 5 (3) (1962) 617–626.
[8] A.O. Maslat, M. Abussaud, H. Tashtoush, M. Al-Talib, Pharmacology 54 (2002) 55–59.
[9] A.A. Farghaly, A.A. Bekhit, J.Y. Park, Arch. Pharm. (Weinheim) 333 (2000) 53–57.
[10] Song Cao, Xu Hong Qian, Gonghua Song, Bing Chai, Zhisheng Jiang, J. Agric. Food Chem. 15 (2003) 152–155.
[11] S.N. Pandeya, A Text Book of Medicinal Chemistry. S.G. Publisher, Varanasi, 2001, 353p.
[12] B.S. Furniss, A.J. Hannaford, V. Rogers, P.W.G. Smith, A.R. Tatchell, Vogel's Text Book of Practical Organic Chemistry, fourth ed. ELBS publication/Longman, London, 1978, 841p.
[13] Mackie, Mc. Cartney, in: J.G. Collee, J.P. Duguid, A.G. Fraser, B.P. Marmion (Eds.), Practical Medicinal Microbiology, 13th ed. (1989), p. 87.